An Unusual Systemic Staphylococcal Illness With Features of the Mucocutaneous Lymph Node Syndrome

KAREN S. SERVILLA, MD
JON A. GREEN, MD, PhD
H. JAMES WILLIAMS, MD
JOHN J. ZONE, MD
Salt Lake City

STAPHYLOCOCCI PRODUCE several distinct but related diseases, including the scalded skin syndrome, bullous impetigo, a scarlet fever-like illness and the staphylococcal toxic shock syndrome. These individual staphylococcal syndromes share many features in common. Often the assignment of a definitive diagnosis to a specific staphylococcal illness is complicated by the multiplicity of separate syndromes, the relative paucity of diagnostic criteria and the absence of definitive laboratory tests.[1]

The mucocutaneous lymph node syndrome is a disease of unknown cause that shows many of the characteristics of a staphylococcal toxin-mediated systemic disease.[2] Epidemiologic, immunologic and clinical features support the existence of an infectious agent in the early stages of the illness.[3,4] The mucocutaneous lymph node syndrome has a pronounced predilection for the younger pediatric population, which is emphasized by the rare occurrence of any similar disease in older persons.[5] Arguably, the mucocutaneous lymph node syndrome is a disease only of children, and similar illnesses in adults are by definition variants of other staphylococci-mediated processes. The report of the occurrence in an adult of an unusual systemic disease with features of this syndrome, as well as of staphylococcal toxic shock syndrome and staphylococcal scarlet fever, underscores the diagnostic dilemmas imposed by the protean clinical presentation of the systemic staphylococcal syndromes, and affords insights into the possible cause of the mucocutaneous lymph node syndrome.

Report of a Case

The patient, a 35-year-old woman previously in good health, was transferred from another hospital to the University of Utah Medical Center with an illness characterized by 15 days of fever, progressive malaise, arthralgias and myalgias. At the time her illness began, the patient was a vigorous, athletic mother of one who was not menstruating, did not use tampons and who had no known environmental exposures resulting in her symptoms.

Ten days before the onset of the illness, the patient noted painful erythematous vesicles over the pretibial regions. These lesions resolved spontaneously over four to five days. Subsequently a nonpruritic, reticular rash developed on the right thigh. A few days later the patient had fatigue, fever, chilling with rigors, headaches, myalgias, right knee pain and bilateral axillary pain. She was admitted to hospital at another institution.

In Figure 1 is summarized the clinical course of the first and second hospital admissions. On initial evaluation the patient appeared ill and had a blood pressure of 115/70 mm of mercury and a temperature of 38°C (100.4°F). The leukocyte count was 16,700 per μl with 50% bands, 47% segmented cells, 2% lymphocytes and 1% monocytes. The hematocrit was 37% and the platelet count normal. A Westergren sedimentation rate was 40 mm per hour. A specimen of clean, voided urine contained 1+ protein, 3+ hemoglobin, two to four erythrocytes, three to five leukocytes and one to three epithelial cells per high-power field and a few bacteria. Rheumatoid factor, Monospot slide test for infectious mononucleosis, antistreptolysin 0 titers and febrile agglutinins were negative. An electrocardiogram (ECG) showed minor nonspecific ST-T abnormalities. Culture of specimens from the throat and vagina grew normal flora without staphylococci or pathogenic streptococci. Blood cultures were negative.

The patient was treated with a regimen of indomethacin without improvement. On the second hospital day the temperature by mouth was 39°C (102.2°F). A sore throat, red tongue and ulcerations of the buccal mucosa were noted. An antinuclear antibody titer of 1:640 was reported, a diagnosis of systemic lupus erythematosus was made and therapy with prednisone, 60 mg a day, was instituted. Headaches, myalgias and arthralgias continued and the patient was transferred to the University of Utah Medical Center on the 15th day of her illness.

On admission to the medical center, the patient was lethargic, irritable and complained of muscle pain with slight movements. Her temperature was 36.8°C (98.2°F), pulse 72 beats per minute and blood pressure 130/78 mm of mercury. Photophobia was noted. A prominent diffuse morbilliform rash was apparent on the face, trunk and hands. Erythematous blanching papules were present over the anterior and lateral surfaces of the lower extremities. The oropharynx was erythematous with a small, well-demarcated shallow ulceration on the right tonsillar pillar. The lips and tongue were red and dry. No cervical adenopathy was present, but there was bilateral axillary adenopathy with a tender 3 cm left axillary lymph node. Cardiac examination showed no abnormalities. There were effusions in the knees, ankles and proximal interphalangeal joints and mild swelling of the upper and lower extremities. On musculoskeletal examination she had diffuse weakness due to pain. There were no focal neurologic findings.

A leukocyte count was 16,000 per μl with 84% segmented cells, 2% bands, 1% eosinophils, 11% lymphocytes and 2% monocytes. The hematocrit was 39.1% and the platelet count slightly elevated at 419,000 per μl. The Westergren sedimentation rate was 79 mm per hour. A urine specimen contained an occasional leukocyte and a few bacteria. The serum albumin level was 3.5 mg per dl, and the serum liver and muscle enzymes, blood urea nitrogen and creatinine were within normal limits. The cerebrospinal fluid contained no cells and

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From the Divisions of Infectious Diseases (Dr Green) and Dermatology (Dr Zone), Department of Internal Medicine (Drs Servilla, Green, Williams and Zone) and the Center for Infectious Diseases, Diagnostic Microbiology and Immunology (Dr Green), University of Utah School of Medicine, Salt Lake City.

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Reprint requests to Jon A. Green, MD, Center for Infectious Diseases, Diagnostic Microbiology and Immunology, University of Utah School of Medicine, Salt Lake City, UT 84132.

had a protein of 20 mg per dl. Serologic studies were negative for cytomegalovirus, rubella, rheumatoid arthritis, syphilis, hepatitis B surface antigen and mononucleosis. An antinuclear antibody titer was 1:20. A lupus erythematosus preparation and anti-double-stranded DNA antibody were negative. Complement fixing antibodies to blastomycosis, coccidioidomycosis and histoplasmosis were also negative, as were agglutinating antibodies to *Proteus* OX-2, OX-K and OX-19; *Salmonella* A, B, C, D and E; typhoid O and H; paratyphoid A, B and C, and *Brucella* antigens. Titers for *Mycoplasma*, adenoviruses A and B and *Chlamydia* were not elevated. Serum complement levels were C3, 167 mg per dl; C4, 41 mg per dl, and C3 proactivator (C3PA), 63 mg per dl. The C3 and C3PA were mildly elevated. Results of an ECG were normal. Intradermal delayed hypersensitivity testing for *Candida*, coccidioidomycosis and mycobacteria was negative. Cultures of specimens of blood, cerebrospinal fluid and urine on standard bacterial and fungal media were negative.

The prednisone regimen was discontinued at the time of admission. Over the next day the patient had increasing headaches, myalgias and pharyngitis. Treatment with indomethacin (Indocin) was reinstituted without effect. On the 16th day bilateral, nonexudative, sterile conjunctivitis and lip fissures were noted for the first time. New 1- to 2-mm erythematous papules appeared on the extremities.

Skin biopsy specimens of a new leg lesion showed a superficial lymphohistiocytic infiltrate that was predominantly lichenoid with some perivascular component. There was vacuolar degeneration of basal cells with individually necrotic keratinocytes but no vesicles were seen. Direct immunofluorescence of biopsy specimens obtained from both involved and sun-exposed, uninvolved skin failed to show any evidence of deposition of IgG, IgM, IgA or C3 at the dermal epidermal junctions or around superficial dermal blood vessels. On the basis of this negative "lupus band test" a diagnosis of lupus erythematosus was considered unlikely.

On the 17th day, the patient had pronounced increase in her malaise, myalgias and headaches. A temperature taken orally was 36.6°C (98.0°F) and blood pressure was 138/68 mm of mercury. Despite being afebrile, the patient was immobilized by muscle pain, resisted any movement and was unable to care for herself. Aspiration of the left axillary lymph node, initially thought to be reactive, produced 8 ml of purulent-appearing material that contained many polymorphonuclear leukocytes and Gram-positive cocci in clusters. Treatment with nafcillin sodium, 1 gram every four hours, was started and the indomethacin therapy was discontinued. Culture of the aspirated material subsequently grew *Staphylococcus aureus* sensitive to the penicillinase-resistant penicillins. Total leukocyte count at that time was 18,200 per μl with 12% bands, 66% segmented cells, 1% eosinophil, 1% basophil, 9% lymphocytes and 11% monocytes.

On the 18th day the patient continued to have generalized complaints but remained afebrile. Increased palmar erythema and phalangeal edema were noted, which were accompanied by periungual desquamation of the right index finger. The left axillary adenitis increased despite antibiotic therapy and was surgically incised and drained. An indium In 111 leukocyte scan showed accumulation only in the area of the left axillary node. An echocardiogram showed no valvular or coronary artery abnormalities.

Over the next two days the patient's condition improved. The conjunctival redness, lip fissures and adenitis decreased and the lower extremity lesions resolved. The patient's physical activity and sense of well-being increased dramatically, and she was discharged with a ten-day course of dicloxacillin

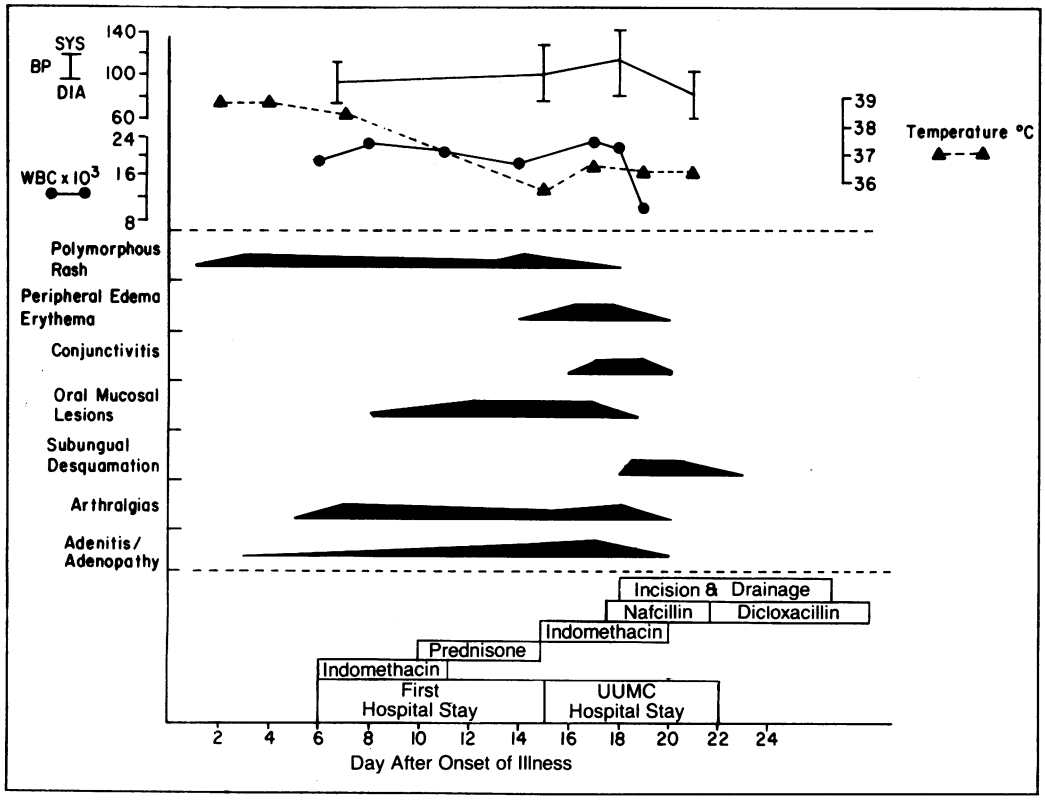

Figure 1.—Clinical course during both hospital admissions. UUMC = University of Utah Medical Center.

sodium on the 22nd day after the onset of her illness. Before discharge the leukocyte count was 8,200 per μl with a normal differential. A Westergren sedimentation rate was 54 mm per hour and an ECG was normal.

Three weeks following discharge she was still fatigued but otherwise symptom-free.

Discussion

This case presents many of the diagnostic and laboratory findings of the mucocutaneous lymph node syndrome.[6] The syndrome is defined by the presence of fever of more than five days' duration, conjunctival injection, oral mucosal changes, induration of the hands and feet, palmar and plantar erythema, periungual desquamation beginning about two weeks after onset of the illness, diffuse erythematous rash and enlarged lymph nodes with at least one node 1.5 cm or larger in diameter.[4,5] The absence of nonsuppurative cervical adenopathy, the presence of staphylococcal axillary adenitis and the age of our patient did not fit the case definition of the mucocutaneous lymph node syndrome.

The patient was showing an advanced degree of morbidity at the time a percutaneous needle aspiration disclosed the presence of a staphylococcal infection. Nevertheless, prompt resolution of constitutional symptoms followed surgical drainage of the affected lymph node and the systemic administration of antistaphylococcal antibiotics. Failure to alter the course of the disease process with antibiotics alone is similar to observations of the lack of utility of appropriately administered antistaphylococcal drugs in cases of the mucocutaneous lymph node syndrome in children with pronounced cervical adenopathy[7] and shows that a failure to respond to antibiotics does not exclude an infectious cause for this or other toxic syndromes.

Identification of a staphylococcal origin of our patient's illness encourages attempts to classify it as one of the existing, recognized toxic syndromes of staphylococcal origin such as a highly atypical variant of the more commonly recognized nonmenstrual staphylococcal toxic shock syndrome.[8,9] Such a diagnosis is supported by the patient's age and sex, a coexisting staphylococcal infection and the multisystem involvement.[10] However, the nature of the multisystem disease mitigates against this diagnosis. In particular, the lack of hypotension, thrombocytopenia, myositis or nephritis makes this diagnosis questionable. It is possible that intermittent therapy with steroids given orally and nonsteroidal anti-inflammatory agents may have altered this patient's clinical course, confusing the diagnosis. Alternatively, the patient's unusual syndrome may be another example of the staphylococcal scarlet fever syndrome. The severe degree of morbidity, lack of scarlatiniform rash and the absence of characteristic dermatopathologic changes consisting of intraepidermal cleavage through desmosomes of the stratum granulosum[11] make this diagnosis unlikely as well.

The exact designation of our patient's staphylococcal syndrome remains unresolved. Cases have been reported previously of adults who had the mucocutaneous lymph node syndrome[12-14] and scarlet fever-like illnesses.[15] Most of these cases involved young women, some of whom were menstruating or had documented staphylococcal infections with significant systemic toxicity. In retrospect, these cases were probably of the staphylococcal toxic shock syndrome.[16] The scalded skin syndrome in children is also occasionally misdiagnosed as the mucocutaneous lymph node syndrome. The pronounced similarity in these syndromes and perhaps their variants are responsible for the difficulty in achieving a diagnosis. Whether a separate syndrome or a variant of the strictly defined mucocutaneous lymph node syndrome, staphylococcal toxic shock syndrome or staphylococcal scarlet fever, the current case has the potential for increasing the understanding of the cause of serious and at times fatal diseases of children and adults.

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